Weight gain is a common concern among aging women. Nearly two-thirds of women ages 40 to 59 years and about three-fourths of women older than 60 years are overweight (body mass index greater than 25 kg/m$^2$) in the United States. Ekta Kapoor, M.B.B.S., a consultant with the Women’s Health Clinic; General Internal Medicine; and Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “Midlife women may gain up to 0.7 kg per year and demonstrate a change in body fat distribution, from the premenopausal gynoid pattern (greater lower-body fat) to the postmenopausal android pattern (greater upper-body fat). Weight gain and body fat distribution changes are responsible, at least in part, for the greater risk of cardiovascular disease in postmenopausal women, in comparison with younger women with intact ovarian function. Cardiovascular disease is the leading cause of mortality in postmenopausal women, and the importance of risk factor modification cannot be overemphasized.”

However, when women ask specifically about the impact of hormone therapy on weight gain during menopause, the answer is much more complicated because of the complex interactions of their symptoms with age-related changes. There has been a debate about the relative contribution of aging versus menopause to weight gain in midlife women. Stephanie S. Faubion, M.D., of the Women’s Health Clinic and General Internal Medicine at Mayo Clinic in Rochester, Minnesota, comments: “The current literature supports the aging theory, and that menopause, per se, after adjustment for aging, does not result in significant weight gain. However, menopause does result in body fat distribution changes, with a preferential deposition of body fat centrally, and an increase in abdominal obesity. This tendency persists despite adjustment for aging, total body fat, and reduced physical activity level, all of which independently increase visceral fat deposition.”

Aging-related weight gain is universal, occurs in both sexes, and is mainly ascribed to the decrease in lean body mass and physical activity level (which may be subtle). These changes result in a fall in both the resting- and activity-related energy expenditure. Therefore, unless there are compensatory changes in dietary habits and physical activity, aging results in weight gain. Alice Y. Chang, M.D., a consultant with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, notes: “Midlife women during the menopausal transition might experience unique symptoms...”
that facilitate weight gain, including vasomotor symptoms, mood disorders, sleep disturbances and musculoskeletal complaints. Perimenopausal women often under estimate the impact of vasomotor symptoms on so many aspects of their lives. For example, women with severe vasomotor symptoms, especially at night, might not realize how severe fatigue compromises their ability to remain active. Women are more prone to mood disorders in the perimenopausal period, and that can also interfere with their motivation to make lifestyle changes often required to prevent weight gain. On the other hand, women who are overweight or obese tend to have worse hot flashes than their normal-weight counterparts, and weight loss improves vasomotor symptoms. Resistance exercise training, which can prevent the muscle loss and may even be protective in energy expenditure related to aging in general, not only is shown to be as effective in perimenopausal women but can also help preserve bone mass during a period of accelerated bone loss and improve musculoskeletal symptoms.”

Dr. Faubion adds: “Menopausal hormone therapy (MHT) is the most effective treatment for menopausal vasomotor symptoms. It should be strongly considered in recently postmenopausal (less than 10 years since last menstrual period) women with moderate to severe vasomotor symptoms in the absence of any contraindication to systemic estrogen use. In the young, recently postmenopausal women without pre-existent cardiovascular disease, low-dose transdermal estradiol does not increase the risk of cardiovascular disease, and may even be protective. Similarly, the risk of breast cancer does not seem to be increased with estrogen monotherapy, but may be higher in regimens using estrogen with synthetic progestogens. However, the current MHT regimens most commonly use micronized progesterone, which does not seem to be associated with the same risk of breast cancer. In addition to alleviation of vasomotor symptoms, MHT also improves sleep and mood for most women, although it is not recommended as primary therapy for sleep or mood disturbances.”

While MHT does not cause any changes in weight by itself, it does result in favorable distribution of body fat. Dr. Kapoor explains: “Women on MHT tend to have redistribution of the central fat to the peripheral sites. However, MHT use is not recommended for prevention or management of weight gain. Women who are on MHT for management of vasomotor symptoms can, nonetheless, be counseled regarding its beneficial effects on body fat distribution. In addition to standard recommendations regarding a hypocaloric diet (500-750 kcal deficit per day), increased intake of whole grains, fruits and vegetables, use of meal replacements, and regular exercise (150-175 minutes per week), patients should be offered psychological support geared toward identification of barriers to change, monitoring behaviors, problem-solving, strategizing and reinforcement. This support can be provided by a psychologist in individual or group settings depending upon the patient’s needs and preferences.”

Dr. Kapoor continues: “Weight-loss medications should be discussed in appropriate situations (BMI > 30 kg/m² or > 27 kg/m² with complications). However, it is important to recognize potential challenges with medication use, including cost, side effects, modest efficacy (5-10 percent weight loss) and potential for weight regain despite continued use. Finally, bariatric surgery (for BMI greater than 40 kg/m² or greater than 35 kg/m² with complications) and endoscopic bariatric therapy (for BMI between 30 and 40 kg/m²) should be considered when appropriate. Endoscopic bariatric therapies comprise the fastest growing treatment for obesity, and offer promise to bridge medical and surgical therapy. However, the procedures continue to evolve and are not routinely covered by insurance. There also is the potential for weight regain after procedures such as intragastric balloon placement.”

So when women ask about the impact of MHT on their weight maintenance and weight-loss goals, MHT cannot be recommended as a therapy to assist in weight loss. However, an individualized assessment should determine whether MHT could have a significant impact on symptoms during the menopausal transition and contribute to overall health.

Dr. Kapoor concludes: “Weight management in midlife women requires a thorough understanding of the menopausal changes, symptoms or both in order to recognize and address potential barriers to implementation of a behavioral program for weight loss. An ideal program follows a multidisciplinary approach, which involves several experts, including medical providers, behavioral psychologists, dietitians, exercise specialists and lifestyle coaches. In addition to recommending lifestyle changes, these providers should carefully screen patients for the presence of menopausal symptoms, including hot flashes, sleeping difficulties and mood problems, and appropriately treat for the conditions. This screening helps improve compliance with behavioral interventions for weight loss.”
Robert J. Nellis with Research and Education Communications at Mayo Clinic in Rochester, Minnesota, recently investigated the beginnings of the therapeutic use of insulin at Mayo Clinic. Nellis says: “Hired in 1919 to run Mayo Clinic’s Diabetes Unit, Dr. Russell M. Wilder had few options in treating patients with type 1 diabetes mellitus, other than an extreme calorie-restricted diet. Some patients were living for three, four or five years after onset, provided they adhered strictly to the feeding regimen. Elizabeth Hughes, daughter of Charles Evans Hughes, the former U.S. chief justice and secretary of state, was kept alive that way. After several years on the treatment, she weighed 45 pounds and was barely able to walk. Another was a 12-year-old boy from Chicago named Randall Sprague, who was kept alive by Dr. Rollin T. Woodyatt, Dr. Wilder’s mentor in Chicago. Fortunately for both patients, medicine was about to change.”

University of Toronto researcher Dr. Frederick G. Banting and medical student Charles H. Best had been experimenting with dogs in the laboratory of Dr. James J.R. Macleod. Their discovery was announced at the American Physiological Society meeting in December 1921 in New Haven, Connecticut. Dr. Wilder wrote in his memoirs: “What a Christmas gift that was — an extract of the pancreas developed at Toronto, which effectively controls the symptoms of diabetes! We learned still more about it at the meeting of the Association of American Physicians in the spring of 1922. Excitement prevailed.” Drs. Banting and Macleod received the Nobel Prize in physiology or medicine in 1923 for the discovery of insulin.

Nellis notes: “Still, no one knew the best strategy to administer insulin to the wide variety of patients who were hanging on to life, some with multiple complications. The Toronto group turned to a handful of top clinical researchers for help. One of those was Dr. Wilder at Mayo Clinic.”

Dr. Wilder wrote: “Samples of insulin were first received at Mayo Clinic in the early spring of 1922. They were for experimental trials ... but an adequate amount of insulin to insure everyone getting it who needed it was not available until the autumn of 1922, and Oct. 1 of that year is the date which divides for us the insulin era from the pre-insulin era.”

Nellis reflects: “It was as if someone had drawn an arbitrary line in the sands of time. Once insulin became available, the line would be crossed. That was when the vast majority of patients with childhood diabetes had their first chance at a relatively normal life. Most people today have no idea how dire a diagnosis of diabetes was in that time.”

Dr. Wilder wrote: “We had 32 children with diabetes in Mayo Clinic between Oct. 1, 1919, and Oct. 1, 1922, a three-year period. One was moribund on arrival; 28 received satisfactory training and a dietary regimen. Nine survived long enough to benefit from insulin. The others died before it came.”

In November 1922, Dr. Wilder traveled to Ontario to attend a meeting of North America’s foremost clinical experts in diabetes at the time. Dr. Wilder’s enthusiasm about the meeting leaps from the page of his notes: “Never again was I to experience a thrill equal to that of being invited to attend the meeting in Toronto of a small committee of experts, called together by professor James J.R. Macleod to undertake an extensive clinical evaluation of the product, insulin.” Over a cold weekend, the experts compared experiences. Dr. Wilder’s notes revealed the following comments:

• “Allen has given one dose every six hours. Campbell gives his dosage 3/4 hour before meals.”
• “Woodyatt — reported a death contributed to by overdosage — no post-mortem. Four other patients receiving same dosages had symptoms but no ill effects.”
• “Gilchrist — has been testing potency of preparations on himself. Reaction — fatigue — preparation increased pulse rate, tremor sensation.”
• “Banting — four children tell that they feel shaky.”
A 68-year-old man was referred to the endocrine clinic for evaluation of abnormal thyroid function tests. His medical history was notable for metastatic malignant melanoma, initially located at the right thigh, for which he underwent wide local excision and extensive lymph node dissection three years earlier. The following year, he developed local recurrence and new pelvic lymphadenopathy, for which he underwent resection followed by radiation therapy. Due to disease progression (BRAF wild type), the patient was initiated on ipilimumab, an immune checkpoint inhibitor targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4). The patient received four cycles of ipilimumab — 3 mg/kg/day every three weeks. His disease...
remained refractory, and he was then initiated on a second immune checkpoint inhibitor targeting programmed death receptor-1 (PD-1), pembrolizumab 2 mg/kg/day every three weeks. As part of surveillance for immune-related adverse events (irAEs), thyroid function tests were checked: TSH = 0.01 mIU/L (normal, 0.3-4.2 mIU/L) and free T4 = 2.2 ng/dL (normal, 0.9-1.7 ng/dL). The patient had moderate fatigue; he denied tremors or palpitations. His family history was significant for a sister with primary hypothyroidism.

Further evaluation in the endocrine clinic demonstrated a normal erythrocyte sedimentation rate and normal levels of TRAB and TPO antibodies. Sonographic examination of the neck demonstrated diffuse heterogeneity of the thyroid gland suggestive of thyroiditis (Figure 1) and low to absent iodine uptake on thyroid scan confirmed thyroiditis (Figure 2). Re-staging imaging for his melanoma with 18F-fluorodeoxyglucose positron emission tomography demonstrated new bilateral thyroid uptake more pronounced on the previously negative left thyroid lobe (Figure 3). Repeat thyroid function tests three weeks later showed progression to overt hypothyroidism: TSH = 13.1 mIU/L, total T3 = 69 ng/dL (normal, 80-200 ng/dL), and free T4 = 0.9 ng/dL. The patient was initiated on levothyroxine replacement therapy and treatment with pembrolizumab was continued.

The immune checkpoint inhibitors pembrolizumab, ipilimumab and nivolumab represent a novel class of immune-directed anti-neoplastic therapies with significant anti-tumor efficacy. These fully humanized, monoclonal antibodies block negative regulatory receptors (for example, CTLA-4 or PD-1) on T cells, resulting in a derepression or re-activation of cytotoxic T cell function or both. Clinically, this translates into durable tumor regression in patients with melanoma, lung cancer, renal cell carcinoma or Hodgkin’s lymphoma. The list of Food and Drug Administration-approved malignancies for treatment with these immune therapies continues to expand as clinical trials in a wide variety of tumor types are demonstrating tumor efficacy.

As expected, however, immune modulators have introduced unique immune-based toxicities. Thyroid abnormalities and hypophysitis are the two most common endocrine irAEs, although primary adrenal insufficiency and type 1 diabetes mellitus have also been reported. The endocrine clinic recently reviewed thyroid abnormalities among cancer patients receiving pembrolizumab. Thyroid dysfunction occurred in approximately 15 percent of patients and most often presented as an acute painless thyroiditis or overt hypothyroidism. The median onset of thyroid abnormalities was

![Figure 1. A. Thyroid ultrasound showing diffuse heterogeneity of the thyroid gland. B. Doppler ultrasound demonstrating increased thyroid vascularity.](image1)

![Figure 2. Thyroid uptake and scan showing diffusely decreased uptake, consistent with thyroiditis. The 23-hour radioactive iodine uptake was 0.6 percent (normal 24-hour uptake = 8-29 percent).](image2)

![Figure 3. 18F-fluorodeoxyglucose positron emission tomography scan of the neck at the level of the thyroid gland. A. Prior to pembrolizumab therapy. B. Six months after pembrolizumab initiation.](image3)
On March 13, 2016, Dr. Henry S. Plummer was inducted into the Health Care Hall of Fame at a ceremony in Chicago. He joins Dr. William J. Mayo and Dr. Charles H. Mayo, who were inducted into the Health Care Hall of Fame in 2009. Dr. Plummer (Figure 1), an endocrinologist at Mayo Clinic from 1901 to 1936, is best known to endocrinologists for the description of toxic multinodular goiter (Plummer’s disease). However, Dr. Plummer was multitalented:

Within the first two to four weeks following treatment initiation with either ipilimumab or pembrolizumab. In accordance with a study published in The Journal of Clinical Endocrinology & Metabolism in 2016, thyrotoxicosis is usually transient with either regain of normal thyroid function or evolution to hypothyroidism. Thyroid autoantibodies are variably elevated in some patients, but most often normal. Rare cases of Graves’ disease and ophthalmopathy have been reported. In current clinical trials published in Current Opinion in Oncology in 2016 and Endocrine-Related Cancer in 2014, thyroid dysfunction is reported in 1 to 15 percent of patients treated with pembrolizumab and 0 to 4 percent of patients treated with ipilimumab. Occasionally, a low TSH may indicate the presence of a central process consistent with immune therapy-induced hypophysitis. Hypophysitis is uncommon with anti-PD-1 therapy and more frequent with anti-CTLA-4 therapy.

Management of immune modulator-induced acute thyroiditis is similar to other etiologies (for example, symptomatic-based therapy with beta-adrenergic blockers, if indicated). Levothyroxine replacement is appropriate for overt hypothyroidism, although some patients may recover thyroid function. The endocrine clinic has commonly observed thyroid hormone abnormalities coincident with new, diffuse increased fludeoxyglucose uptake in the thyroid that resolves on follow-up imaging, suggesting an underlying immune-mediated destructive inflammatory process rather than metastatic tumor spread. Our patient developed frank hypothyroidism and was initiated on levothyroxine replacement therapy while continuing immunotherapy. The underlying mechanism of immune-mediated thyroid dysfunction and the role of thyroid autoantibodies in this anti-thyroid immune response remain unknown.

Conclusions
The indications for immune checkpoint inhibitors for patients with advanced cancer have greatly expanded within the last five years. Endocrinologists and medical oncology teams should be familiar with their unique endocrine-related irAEs in order to minimize morbidity and enable appropriate management, as indicated by research published in Melanoma Research in 2016. Thyroiditis may need supportive care, with monitoring for development of hypothyroidism. Thyroid hormone replacement therapy is often required for immune therapy-induced hypothyroidism, though thyroid recovery may also occur. Importantly, serial measurements of thyroid function tests are indicated, especially during the first weeks of pembrolizumab therapy. Further studies with histopathological correlates are required for a better understanding of the underlying immune cell subtypes that mediate these irAEs. Importantly, there are now ongoing or soon to open clinical trials attempting to harness this anti-thyroid immune response with immune checkpoint inhibitors for patients with advanced, radioiodine refractory thyroid cancer, as well as for anaplastic thyroid cancers.

For more information


He heralded the concept of a comprehensive medical record at Mayo Clinic in which all the information about a patient could be found in one place rather than kept separately by each doctor. He is credited with designing the system that led to the hallmark of Mayo Clinic—a comprehensive, multidisciplinary approach to medical practice.

Dr. Plummer was drawn to medicine at a young age. His father was a country doctor. As a toddler, Henry loved looking at the illustrations in his father’s book *Gray’s Anatomy*. As a child, Henry would accompany his father on house calls.

Dr. Plummer’s interest in innovation started early. While going on house calls by horse and buggy, he devised a system of ropes extending from his house to the barn, allowing him to pull on the rope that tipped the feed bucket so that his horse would be fed by the time he was ready to leave. He went to the University of Minnesota for two years and subsequently received his medical degree from Northwestern University. Dr. Plummer then returned home to help his father in his practice (Figure 2).

Three years later, in 1901, Dr. Plummer was recruited to join Mayo Clinic. He was a gifted internist and endocrinologist, who also recognized how technology, organizational design and architecture could maximize the clinic’s effectiveness. Dr. William J. Mayo would remark that hiring Dr. Plummer was the best day’s work he ever did for the clinic. As Mayo Clinic’s status grew and the time came to move to larger premises, Dr. Plummer took the lead role as chairman of the building committee, committing himself for weeks to study the clinic’s needs and design the most efficient layout for the new 15-story Mayo building. The clinic building was completed in 1928 and subsequently named the Plummer Building (Figure 3).

Other technologies Dr. Plummer introduced to Mayo Clinic include the pneumatic tube system for sending files between buildings, conveyor system and color-coded lights outside exam rooms that indicate the need for special consultants. Dr. Plummer died of a cerebral blood clot in 1936 at age 62. He recognized his illness and gathered his family and told them that he would soon become unconscious. He accurately predicted the outcome and died that evening. In honor of Dr. Plummer’s role as the father of modern clinical records, Mayo Clinic has partnered with Epic Systems Corp. to build a single electronic health record and revenue cycle management system—an initiative named the Plummer Project.

Figure 1. Dr. Henry S. Plummer.

Figure 2. Dr. Henry S. Plummer at age 26, after receiving his medical degree from Northwestern University, Evanston, Illinois.

Figure 3. Photograph from 1928 showing the Plummer Building in Rochester, Minnesota. When construction was completed, it was the tallest building in Minnesota.
Education Opportunities

20th Annual Mayo Clinic Endocrine Update 2017
Jan. 30-Feb. 3, 2017, at The Ritz-Carlton, South Beach, Miami Beach, Fla.

Designed for endocrinologists and interested internists and surgeons, this course addresses gaps in medical knowledge and barriers in clinical practice to improve the outcomes of patients with endocrine and metabolic disorders. Topics span the full range of endocrinology through lectures, debates, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast roundtable discussions and small-group discussions with experts. Attendees have plenty of opportunity for interaction with the course faculty, who are selected for their expertise and clinical acumen. For more information, visit https://ce.mayo.edu/endocrinology/content/20th-annual-mayo-clinic-endocrine-update-2017 or call 800-323-2688 (toll-free).

17th Annual Nutrition and Wellness in Health and Disease 2017
Sept. 25-26, 2017, at Park Central San Francisco

This course is designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness staff. Many physicians and other clinicians have had limited training in nutrition, yet nutrition is key to the management of many endocrine disorders, such as diabetes, obesity and lipid disorders. In addition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. Participants will discuss situations commonly encountered in the ambulatory setting. Topics include obesity in adults and children, individual and group-based weight management strategies, and dietary, behavioral change, activity, pharmacologic and bariatric approaches. Additional topics include nutrition and physical activity management of common obesity-associated conditions plus physical activity and wellness topics for attendees and their patients. Presentations offer practical clinical management pearls, interactive case studies and panel discussions. For more information, visit http://ce.mayo.edu/nutrition2017 or call 800-323-2688 (toll-free). Course hashtag: #MayoNutrCME.